

Antimicrobial therapy of pediatric patients with sinusitis

Ellen R. Wald, MD Pittsburgh, Pa.

The mainstay of medical therapy for acute and subacute sinusitis is the selection of an antimicrobial agent based on an appreciation of the usual bacterial pathogens that include Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. Amoxicillin is appropriate therapy for patients with uncomplicated sinusitis in geographic areas in which the prevalence of β -lactamase-producing pathogens is less than 20%. If a patient does not respond to amoxicillin or in areas in which there is a high prevalence of β -lactamase-producing bacterial species, alternative antimicrobials include amoxicillin-clavulanate, erythromycin-sulfisoxazole, trimethoprim-sulfamethoxazole, cefaclor, cefuroxime axetil, and cefixime. Cefixime, which is less active against S. pneumoniae than most of these antimicrobials, should be reserved for patients who do not improve with amoxicillin. Amoxicillin-potassium clavulanate, cefuroxime axetil, and erythromycin-sulfisoxazole have the most comprehensive antibacterial spectra. (J ALLERGY CLIN IMMUNOL 1992;90:469-73.)

Key words: Sinusitis, antimicrobial therapy, antibiotic therapy

The mainstay of medical therapy for acute sinusitis is the use of antimicrobial agents. The selection of an antimicrobial agent requires an appreciation of the usual bacterial pathogens responsible for sinus infection. In the case of acute sinusitis, which is defined as disease of less than 30 days' duration, the common bacterial isolates are *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* in a relative prevalence of 30%, 20%, and 20%, respectively.¹ Currently, in Pittsburgh, approximately 75% of *M. catarrhalis* and 30% of *H. influenzae* can be assumed to be β -lactamase producing. Accordingly, about 20% of maxillary sinus pathogens will be resistant to amoxicillin.

In the case of subacute sinusitis, which is defined as disease lasting 30 to 120 days, the common bacterial isolates are again *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae* in roughly equal proportions. Antimicrobial selection will be based on considerations similar to those for patients with acute sinusitis.

COMPARISON OF TREATMENT REGIMENS

Table I shows those antimicrobial agents that have been compared in the treatment of children with sinusitis in published studies or abstracts.¹⁻⁵ Theoretically,

Abbreviation used

SMX-TMP: Sulfamethoxazole-trimethoprim

cally, antimicrobial agents that are effective against β -lactamase-producing bacterial species should offer a therapeutic advantage over amoxicillin in treating 20% of the bacterial isolates responsible for sinusitis. However, it is known that patients with acute sinusitis have a spontaneous cure rate of approximately 40%.³ Therefore about half (10%) of patients who harbor β -lactamase-producing organisms in their maxillary sinuses will recover even when not receiving an optimal antimicrobial agent. Accordingly, we can expect to see at most about a 10% difference between regimens that are effective and those that are ineffective against β -lactamase-producing bacterial species. To demonstrate a 10% difference between any two treatments requires the study of many hundreds of patients in each group of a controlled trial. Most studies of antimicrobial efficacy have involved small numbers of patients, usually between 25 to 30 patients. Therefore not surprisingly, most antimicrobial agents have appeared to perform similarly in studies that evaluated the clinical outcome of patients with sinusitis.

Unfortunately, no studies have been performed in children in whom bacteriologic efficacy has been assessed by sinus aspiration and culture after treatment has been initiated. However, studies performed in adult patients with sinusitis have provided valuable information that is probably applicable to children.⁶⁻¹¹

From the University of Pittsburgh School of Medicine and Children's Hospital of Pittsburgh, Pittsburgh, Pa.

Reprint requests: Ellen R. Wald, MD, Professor of Pediatrics, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, 3705 Fifth Ave., Pittsburgh, PA 15213.

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TABLE I. Clinical studies of antibiotics for maxillary sinusitis in children

Reference No.	Drugs and dosage regimen	Clinical cure	
		No.	%
1	Amoxicillin, 40 mg/kg/day, in 3 divided doses	22/27	81
	Cefaclor, 40 mg/kg/day, in 3 divided doses	18/23	78
2	Cefaclor, 40 mg/kg/day, in 3 divided doses	11/12	92
	Amoxicillin-potassium clavulanate, 40/mg/kg/day, in 3 divided doses	16/17	93
3	Amoxicillin, 40 mg/kg/day, in 3 divided doses	20/30	67
	Amoxicillin-potassium clavulanate, 40/mg/kg/day, in 3 divided doses	18/28	64
4	Amoxicillin, 50 mg/kg/day, in 4 divided doses	22/22	100
	Erythromycin-sulfisoxazole, 50/150 mg, in 4 divided doses	21/22	95
5	Amoxicillin, 40 mg/kg/day, in 3 divided doses	17/22	77
	Erythromycin ethylsuccinate, 30-40 mg/kg/day, in 4 divided doses	8/22	36
	SMX-TMP, 40/8 mg/kg/day, in 2 divided doses	13/21	62

TABLE II. Antimicrobials and dosage schedules for the treatment of sinusitis in children

Antimicrobial	Dosage
Amoxicillin	40 mg/kg/day in 3 divided doses
Amoxicillin-potassium clavulanate	40/10 mg/kg/day in 3 divided doses
Erythromycin-sulfisoxazole	50/150 mg/kg/day in 4 divided doses
SMX-TMP	40/8 mg/kg/day in 2 divided doses
Cefaclor	40 mg/kg/day in 3 divided doses
Cefuroxime axetil	250 or 500 mg in 2 divided doses
Cefixime	9 mg/kg/day in 1 dose

CHOICE OF ANTIMICROBIAL THERAPY FOR SINUSITIS

Table II shows a list of suggested antimicrobial agents and dosage schedules for use in pediatric patients with acute sinusitis. All except cefixime have been used in published studies of children with sinusitis.

Amoxicillin is the drug of choice in patients who have uncomplicated sinusitis. Amoxicillin has largely replaced ampicillin in the treatment of bacterial complications of upper respiratory tract infections. Amoxicillin is twice as well absorbed as ampicillin and has a longer half-life. Accordingly, it can be prescribed in half the dose of ampicillin and three rather than four times daily. Amoxicillin is effective in most patients, relatively inexpensive, and most important safe. Safety must be a prime consideration when treating a condition that has a spontaneous cure rate of

40%. The only disadvantage of amoxicillin is its susceptibility to the action of the β -lactamases produced by some *H. influenzae* and *M. catarrhalis*. To overcome this problem, Augmentin, an oral agent in which amoxicillin is combined with potassium clavulanate, was developed and first marketed in 1985. Potassium clavulanate is the salt of clavulanic acid, a β -lactam that barely has any activity against bacterial pathogens but is capable of effective inhibition of β -lactamase enzymes. Amoxicillin-potassium clavulanate is equivalent to amoxicillin alone in activity against amoxicillin-susceptible organisms. The addition of clavulanic acid extends the spectrum of amoxicillin to include β -lactamase-producing strains of *H. influenzae*, *M. catarrhalis*, *Staphylococcus aureus*, and anaerobic bacteria. Amoxicillin-potassium clavulanate causes gastrointestinal symptoms such as abdominal pain, nausea, and diarrhea; however, the diarrhea is often tolerable, and if not, it is immediately and predictably reversed when the agent is discontinued.

Erythromycin-sulfisoxazole is a combination oral agent that has an appropriate spectrum for the treatment of sinusitis in children. Erythromycin, which is effective against gram-positive cocci, cannot be used alone in the treatment of acute sinusitis because it provides inadequate coverage for *H. influenzae*, an important etiologic agent in all age groups. Erythromycin-sulfisoxazole is usually recommended to be administered four times daily and has the potential for gastrointestinal discomfort and hypersensitivity to the sulfa component. The latter, although infrequent, is more serious and potentially less easily reversed than the toxicity observed with β -lactams.

SMX-TMP is another alternative option for oral treatment. The combination of these two folic acid antagonists provides a broad spectrum of antimicro-

bial activity. SMX-TMP is inexpensive and is given only twice daily. Once again sulfa hypersensitivity is a potential problem. Moreover, SMX-TMP does not provide adequate antimicrobial coverage for group A streptococci. This may be an important coinfecting organism in approximately 20% of patients with acute sinusitis.³ Of interest, *S. pneumoniae* has recently been reported to demonstrate increasing resistance to SMX-TMP in communities in which SMX-TMP is frequently used to treat respiratory tract infections. In a recent prospective study of children in day care, the prevalence of SMX-TMP-resistant *S. pneumoniae* increased from 5% in 1979 to 30% in 1984.¹² The emergence of resistance among *S. pneumoniae* may eventually limit the usefulness of this combination antimicrobial agent.

The cephalosporins are antimicrobial drugs that are structurally similar to the penicillins and are also classified as β -lactam antimicrobials. They have been categorized as first-, second-, and third-generation agents according to their time of introduction and similarity of in vitro characteristics. The first-generation cephalosporins lack sufficient activity against *H. influenzae* and therefore are not attractive for use in the treatment of otitis media or sinusitis. Cefaclor, a second-generation cephalosporin, has been a popular oral drug for the treatment of respiratory tract infections in children in part because of its pleasant taste. Unfortunately, cefaclor is susceptible to the action of the β -lactamases produced by most strains of *M. catarrhalis* and some strains of *H. influenzae*. When given twice daily for otitis media, the bacteriologic efficacy of cefaclor was only 71% compared with 90% for SMX-TMP.¹³ A bacteriologic cure was achieved only once when cefaclor, 500 mg twice daily, was prescribed for five adults with acute sinusitis.⁶ These data suggest that when cefaclor is prescribed, a three times daily regimen is preferred. Cefaclor has also been associated with a serum sickness-like reaction in children who have received multiple courses of the drug. The incidence of this reaction is approximately 1.0%.¹⁴

In contrast to cefaclor, cefuroxime axetil, another second-generation cephalosporin, is a very attractive option for the treatment of older children with sinusitis who require an antimicrobial agent that has a more expanded spectrum than amoxicillin. When cefaclor at 500 mg three times daily was compared with cefuroxime axetil at 250 mg twice daily in the treatment of acute maxillary sinusitis in adults, the bacteriologic cure rates were 71% and 95%, respectively ($p < 0.05$, Fisher's exact test).⁹ Cefuroxime is resistant to the action of the β -lactamases produced by *H. influenzae*, *M. catarrhalis*, and *S. aureus*. In its parenteral form, it has enjoyed much popularity in the

treatment of serious infections of the upper and lower respiratory tracts of children. Unfortunately, in oral form, cefuroxime axetil is only available as a tablet (125, 250, and 500 mg), thereby limiting its usefulness in young children. Although the 125 mg tablets are small, they are very bitter tasting if crushed. The administration of cefuroxime axetil is associated with gastrointestinal toxicity that is similar in type and frequency to that observed with amoxicillin-potassium clavulanate.

Cefixime is a third-generation oral cephalosporin that is administered once daily. There has been no published study of the use of cefixime in patients with acute sinusitis. However, cefixime has been evaluated in the treatment of children with acute otitis media. Its activity against *S. pneumoniae* is less than that of the other antimicrobial agents listed in Table II, although it is quite effective against β -lactamase-producing *M. catarrhalis* and *H. influenzae*.¹⁵ Accordingly, it should be reserved for use in children in whom *S. pneumoniae* is no longer a suspected pathogen because of prior treatment with an agent such as amoxicillin, which is consistently active against *S. pneumoniae*.

One additional potential concern in selecting an antimicrobial regimen for patients who have sinusitis is infection with anaerobes. However, these organisms are uncommon isolates in children who have acute and subacute sinus infection.^{1, 16} They should be considered in youngsters either who have very protracted symptoms or who require surgical intervention. The gram-positive anaerobic streptococci and staphylococci are generally penicillin susceptible and therefore do not present a problem. Virtually all the therapeutic regimens discussed will be satisfactory. The gram-negative *Bacteroides* species that produce β -lactamase should respond nicely to amoxicillin-potassium clavulanate.

Although amoxicillin is the drug of choice for patients who have uncomplicated sinusitis, alternative agents must be selected for patients who fail to respond to or are allergic to amoxicillin. The most suitable choices with the most comprehensive spectra are erythromycin-sulfisoxazole in young children and cefuroxime axetil in patients who are able to swallow a tablet.

DURATION OF THERAPY

Duration of antimicrobial therapy for patients with sinusitis has not been studied systematically. Empirically, a 10- to 14-day course of antimicrobial agents is recommended for patients with acute sinusitis. Most patients respond briskly to appropriate antimicrobial therapy; cough and nasal discharge will improve in

48 to 72 hours; if fever is present initially, it will diminish or resolve completely in the same time frame as will disturbances in appetite and sleep patterns. Accordingly, a 10-day regimen usually treats most patients for 7 days beyond the time at which they improve substantially or become symptom free. If patients have not improved within 72 hours of initiation of antimicrobial drugs, an alternative agent should be selected.

If patients have improved slowly but are not yet without symptoms by the tenth day of treatment, antimicrobial therapy should be extended for an additional 7 days. When patients have very protracted symptoms, they often require longer courses of antimicrobial treatment. It may be a good rule of thumb to extend the course of antimicrobial therapy for 1 week beyond the time when symptoms have completely resolved in all patients with sinusitis. It is hoped that this will lead to complete eradication of bacterial colonization in a sinus mucosa that may not yet be restored to normal.

RECURRENT SINUSITIS

Some children with acute sinusitis experience closely spaced recurrent infections. The most common risk factor for recurrent episodes of acute sinusitis is recurrent, closely spaced, viral upper respiratory tract infections. Contacts at day care or older siblings in the home may be the source of these recurrent viral infections.

Other risk factors or underlying problems to consider in patients with recurrent or persistent sinusitis are allergy, an immunodeficiency disorder (insufficient or dysfunctional immunoglobulins),¹⁷ cystic fibrosis, ciliary dyskinesia,¹⁸ or anatomic abnormalities. One can readily screen for immunoglobulin deficiencies and cystic fibrosis. Except for allergy, the remaining problems are uncommon and furthermore not readily remediated.

Preventive strategies for management of recurrent acute sinusitis have not been evaluated. Extrapolating from experience gained in the management of recurrent acute otitis media, it is tempting to consider antimicrobial prophylaxis for these patients.¹⁹ Criteria to be fulfilled before the initiation of antimicrobial prophylaxis might be similar to those frequently recommended for patients with recurrent otitis media; that is, three episodes of sinusitis in 6 months or four episodes in a year. This approach needs to be systematically evaluated in comparison with placebo. Selection of an antimicrobial agent for prophylaxis as well as duration of prophylactic treatment will likewise necessitate careful investigation. Currently, a multicenter evaluation of cefuroxime axetil versus placebo

for prophylaxis of sinusitis in allergic patients who have had recurrent disease is underway.

Occasionally the physician encounters a situation in which symptoms of sinusitis linger despite several long courses of antibiotic therapy that should have been adequate for the anticipated pathogens. A variety of antimicrobial interventions have been instituted. There are anecdotal reports of success with clindamycin alone or in conjunction with amoxicillin-potassium clavulanate or a cephalosporin. Rifampin has been added as a way to increase both the antimicrobial spectrum and drug tissue concentration. Intravenous third-generation cephalosporins have been used, sometimes in combination with intravenous clindamycin. None of these interventions has been systematically evaluated.

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DISCUSSION

Comment. One topic on which we initiated a discussion was the definition of sinusitis. I believe that there is a natural progression on which we have not followed through. However, if we examine the outcome of various therapies, we must have not only a workable definition but a staging system of sinus disease. One thing to which I alluded in my presentation was predicting outcome. We believe that staging sinus disease in a uniform fashion will help us compare data for prophylaxis and that we must have some objective way to compare groups based on their starting point. We also think that the extent of disease, regardless of the underlying cause, is an important way to begin to compare these groups.

If you accept the premise that one of the major causes

of chronic sinusitis is the osteomeatal complex, then a logical way to provide prophylaxis against exacerbations of chronic sinusitis is a combination of antibiotics and antiinflammatory agents. For that reason we use long-term prophylactic medication, such as mucoevacuants and nasal steroids. Again, no data are available, but I question the use of long-term antibiotic therapy alone without addressing the primary disease at the ostiomeatal complex.

Dr. Shapiro. I want to ask Dr. Wald's opinion on the child who has a 2- to 3-day history of nasal discharge and cough after completion of a 3-week course of antibiotics. These are the types of patients in whom we will start prophylaxis after several 3-week courses of treatment.

Dr. Wald. I believe that there are two alternative explanations for a child who has a relapse in symptoms within 3 days. First, you have not adequately eradicated the organism. However, what I see more commonly after a relatively prolonged duration, for example, 20 days, is that 1, 2, 3 or weeks may pass until the child contacts the next cold, and bingo, he/she has the next episode of sinusitis. In this instance it is not inadequate therapy, or a relapse per se but a reinfection. Moreover, in those cases I would probably proceed as you do, that is, give the patient another course of presumably eradicated therapy and then start prophylactic therapy when the patient is as clean as possible.

I believe that you start with the easiest, least morbid course. I consider antibiotic prophylaxis less morbid than general anesthesia. I usually use intranasal steroids if I think allergic rhinitis is a contributing factor. I usually determine this by the fact that although children show substantial improvement while receiving antimicrobials, they never really become symptom free. They have persistent nasal congestion. The physical examination helps me because the turbinates are very swollen and often times pale. I will start a double-pronged approach in these patients. It is reasonable to anticipate that if you successfully treat the nasal membranes, you will not need antimicrobial agents after a short time.